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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,735	07/23/2007	Thomas E. Daley	11594-003-999	3147

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EXAMINER	
WEBSTER, DAVID D	
ART UNIT	PAPER NUMBER
4121	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,735	DALEY, THOMAS E.	
	Examiner	Art Unit	
	DAVID D. WEBSTER	4121	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The application 4-Methylpyrazole Formulations for Inhibiting Ethanol Intolerance, Application10/591735 priority date Aug 31, 2006. An application which claims priority from PCT US 2005/007273 /or non-provisional from the provisional applications on 60/550,261 of March 3, 2004 and 60/642, 007 of January 6, 2005.

The application 10/591735 filed on August 31, 2006 is the national stage entry for PCT/US05/07273 filed on March 3, 2005. The application dates for the application(s) clearly falls within of the 16 month filing date the MPEP 201.13, 35 USC 119(a)-(d) and (f) and 37 CFR 1.55 right of priority of foreign application is accepted.

The date of priority for the application is 03/03/2005

Claims 1-20 are pending.

Restriction/Election

Restriction to one of the following inventions is required under 35 U.S.C. 121 and 372:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I. Claims 1-13, drawn to method of preventing or amelioration a symptom, classified in class 514, subclass 162, 172, 704.

Group II. Claims 14-20, drawn to article of manufacture, classified in class 424, subclass 464, 1.65, 408.

The inventions are distinct, each from the other because of the following reasons:

Groups I and II are related as method of preventing or ameliorating and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case, Group I can be used in or as an intermediate or feeder stock component in an organic synthesis procedure.

Because a search of any or these two distinct inventions would not be co-extensive with a search of the others, an examination and search of two or more inventions in a single application would constitute a serious undue burden on the examiner.

1. The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: there are two distinct inventive concepts.

2. As set forth in Rule 13.1 of the Patent Cooperation Treaty (PCT), "the international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept." Moreover, as stated in PCT Rule

13.2, "where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features." Furthermore, Rule 13.2 defines "special technical features" as "those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art."

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of Group I is method of preventing or amelioration a symptom. The method of preventing or amelioration a symptom of claim 1 does not present a contribution over the prior art.

As disclosed in Japanese patent application JP 57106620 A, the use of 4-methylpyrazole. The 620 application teaches these elements: Page 4 (labeled 118) of application “in three adult males, known to exhibit facial flushing and discomfort symptoms such as tachycardia, palpitations and headache upon drinking….. 55 to 60 kg..... orally administered 250 mg of 4-methylpyrazole hydrochloride dissolved in 50 ml water …….. 15 minutes before administration of 150 ml of sake…….they were observed for symptoms for a period of two hours after the start of drinking …….. they hardly exhibited any facial flushing and did not develop the aforementioned discomfort symptoms. In view of Japanese patent application JP 57106620 as stated above the

method of preventing or amelioration a symptom of instant claim 1 is not novel. As such, Group I does not share a special technical feature with the instant claims of Groups I and II. Therefore, the claims are not so linked within the meaning of PCT Rule 13.2 so as to form a single inventive concept, and unity between Groups I and II is broken.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with inventor's attorney Roger Rich, # 54398, docket number 11594-003-999, of the firm Jones Day; 222 East 41st Street, New York, NY on 12/10/2008 a provisional election was made with traverse to prosecute the invention of group I, claims 1-13. Affirmation of this election must be made by applicant in responding to this office action. Claims 14 - 20 are withdrawn from further consideration by the Examiner, 37 CFR 1.42(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor or at least one claim remaining in the application. Any amendment of the inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48 (b) and by the fee required under 37 CFR 1.17 (h).

35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-5 and 7-13 are rejected under 35 U.S.C. § 102 (b) as being unpatentable over the reference Japanese patent application S57-106620(5), as evidenced by Jacobsen et al., Alcoholism: Clinical and Experimental Research, Vol. 20, pages 804-809 (both references cited by in the IDS submitted on 11-7-06).

Claim 1 recites a method for preventing or amelioration symptom of ethanol intolerance in a subject with reduced or absent aldehyde dehydrogenase subtype 2 (ALDH2) activity comprising orally administering to the subject about 1 to about 4 mg 4-methylpyrazole (4-MP) per kilogram of the subject's body mass.

The 620 application teaches these elements: Page 4 (label 118) of application "in three adult males, known to exhibit facial flushing and discomfort symptoms such as tachycardia, palpitations and headache upon drinking….. 55 to 60 kg..... orally administered 250 mg of 4-methylpyrazole hydrochloride dissolved in 50 ml water ……..

15 minutes before administration of 150 ml of sake…….they were observed for symptoms for a period of two hours after the start of drinking …..... they hardly exhibited any facial flushing and did not develop the aforementioned discomfort symptoms." Furthermore, since there is a direct correlation to the above associated symptoms being exhibited after the ingestion of ethanol in individuals who have reduced or absent ALDH2; direct correlation to the loss of exhibited symptoms and treatment with 4-methylpyrazole is noted as proof of the effectiveness of 4-methylpyrazole.

Claim 3 recites the method of Claim 1, wherein 4-MP is administered in a physiologically acceptable salt form.

The 620 application teaches these elements on Page 2 - 4 (labeled 116-118) of application "in three adult males, known to exhibit facial flushing and discomfort symptoms such as tachycardia, palpitations and headache upon drinking….. 55 to 60 kg..... orally administered 250 mg of 4-methylpyrazole hydrochloride dissolved in 50 ml water.

Claim 4 recites the method of Claim 1, wherein 4-MP is orally administered before the subject consumes ethanol.

The 620 application teaches these elements on Page 2 – 4(labeled 118) of the application. There was a clinical trial stated in application 620 testing the effectiveness of 4-methylpyrazole three males who were known after the consumption of ethanol had displayed the symptoms associate with individuals who are ALDH2 deficient "in three adult males, known to exhibit facial flushing and discomfort symptoms such as

tachycardia, palpitations and headache upon drinking….. 55 to 60 kg..... orally administered 250 mg of 4-methylpyrazole hydrochloride dissolved in 50 ml water.

Claim 5 recites the method of Claim 4 wherein 4-MP is orally administered about one hour to about fifteen minutes before the subject consumes ethanol.

The 620 application teaches these elements on Page 4 (label 118) of application "in three adult males, known to exhibit facial flushing and discomfort symptoms such as tachycardia, palpitations and headache upon drinking….. 55 to 60 kg..... orally administered 250 mg of 4-methylpyrazole hydrochloride dissolved in 50 ml water …….. 15 minutes before administration of 150 ml of sake…….they were observed for symptoms for a period of two hours after the start of drinking …….. they hardly exhibited any facial flushing and did not develop the aforementioned discomfort symptoms."

Claim 7 recites the percent reduction in the subject's ethanol elimination rate is no more than about 10% in comparison to the ethanol elimination rate of a subject not administered 4-MP. or wherein the subject with reduced of absent ALDH2 activity exhibits a percent reduction in ethanol elimination rate that is no more than about 10% in comparison to the ethanol elimination rate of a subject not administered 4-MP (claim 9).

While the '620 publication does not explicitly address this limitation, However, Jacobsen et al., teaches that lower doses of 4-MP (5mg/kg) was effective in treatment but yet did not have the undesirable side effects of larger doses of 4-MP, such as decreased ethanol elimination rate. Since the amount given by the '620 publication was less than that given by Jacobsen et al, it would inherent in the '620 publication that no

more about than 10% ethanol elimination occurred, absent Applicant's evidence to the contrary.

Claim 8 recites the method of preventing or reducing a symptom associated with acetaldehyde accumulation accompanying ethanol consumption in a subject with reduced or absent aldehyde dehydrogenase subtype 2 (ALDH2) activity comprising administering an effective amount of 4-MP that reduces acetaldehyde accumulation by about 50% to about 60% as compared to a subject not administered 4-MP.

The 620 application teaches these elements "page 2 (pg116) the aldehyde accumulation levels in alcohol intolerant persons is mainly governed by the rate of oxidation of alcohol to aldehyde (it is noted that it is well recognized that the form of aldehyde accumulation in alcohol metabolism is acetaldehyde) i.e. by ADH activity, page 3 (pg 117) the us of 50% inhibitory concentration (ID50) of 4-methylpyrazole against human……but as discussed above.....page 4 flushing and discomfort symptoms such as tachycardia, palpitations and headache upon drinking….. 55 to 60 kg..... orally administered 250 mg of 4-methylpyrazole hydrochloride dissolved in 50 ml water …….. 15 minutes before administration of 150 ml of sake…….they were observed for symptoms for a period of two hours after the start of drinking …….. they hardly exhibited any facial flushing and did not develop the aforementioned discomfort symptoms." These same individuals when they are not administered 4-MP have been repeatly noted to exhibit the symptoms addressed above.

to the ethanol elimination rate of a subject not administered 4-MP (claim

Claim 9 recites wherein the subject with reduced of absent ALDH2 activity exhibits a percent reduction in ethanol elimination rate that is no more than about 10% in comparison 9)

While the '620 publication does not explicitly address this limitation, However, Jacobsen et al., teaches that lower doses of 4-MP (5mg/kg) was effective in treatment but yet did not have the undesirable side effects of larger doses of 4-MP, such as decreased ethanol elimination rate. Since the amount given by the '620 publication was less than that given by Jacobsen et al, it would inherent in the '620 publication that no more about than 10% ethanol elimination occurred, absent Applicant's evidence to the contrary.

Claim 10 recites A method of amelioration a symptom of acetaldehyde accumulation accompanying ethanol consumption in a subject with reduced or absent aldehyde dehydrogenase subtype 2 (ALDH2) activity comprising administering an amount of 4-MP or a physiologically acceptable salt of 4-MP effective to reduced or inhibit ethanol –oxidizing activity of alcohol dehydrogenase in the subject.

The 620 application teaches these elements on page 2 (pg116) the aldehyde accumulation levels in alcohol intolerant persons is mainly governed by the rate of oxidation of alcohol to aldehyde i.e. by ADH activity, but as discussed above.....page 4 flushing and discomfort symptoms such as tachycardia, palpitations and headache upon drinking….. 55 to 60 kg..... orally administered 250 mg of 4-methylpyrazole hydrochloride dissolved in 50 ml water …….. 15 minutes before administration of 150 ml of sake…….they were observed for symptoms for a period of two hours after the start of

drinking …….. they hardly exhibited any facial flushing and did not develop the aforementioned discomfort symptoms." Within the 620 application on page 2 (labeled 116) in the second paragraph they have directly associated the physical symptoms with the increase of aldehyde, therefore since the physical effects of aldehyde toxicity were decreased in these patients treated with 4-MP, and accumulation of aldehyde occurs due to the increased ethanol oxidizing activity of alcohol dehydrogenase in these patients, it was inherent in the method taught by the '620 application that the ethanol-oxidizing inhibiting of alcohol dehydrogenase was reduced or inhibited since the effects of aldehyde accumulation were reduced.

Claim 11 recites the method of Claim 8 or 10, wherein a symptom of acetaldehyde accumulation in the subject with reduced or absent ALDH2 activity is selected from the group consisting of flushing, elevated heart rate, palpitations, hypotension, nausea, dizziness, and headache.

The 620 application teaches these elements "page 2 (pg116) the aldehyde accumulation levels in alcohol intolerant persons is mainly governed by the rate of oxidation of alcohol to aldehyde i.e. by ADH activity, but as discussed above.....page 4 flushing and discomfort symptoms such as tachycardia, palpitations and headache upon drinking….. 55 to 60 kg..... orally administered 250 mg of 4-methylpyrazole hydrochloride dissolved in 50 ml water …….. 15 minutes before administration of 150 ml of sake…….they were observed for symptoms for a period of two hours after the start of drinking …….. they hardly exhibited any facial flushing and did not develop the aforementioned discomfort symptoms."

Claim 12 recites the method of Claim 10 wherein an effective amount of a hydrochloride salt of 4-MP is administered.

The 620 application teaches these elements on Page 4 (label 118) of application "in three adult males, known to exhibit facial flushing and discomfort symptoms such as tachycardia, palpitations and headache upon drinking….. 55 to 60 kg..... orally administered 250 mg of 4-methylpyrazole hydrochloride dissolved in 50 ml water …….. 15 minutes before administration of 150 ml of sake…….they were observed for symptoms for a period of two hours after the start of drinking …….. they hardly exhibited any facial flushing and did not develop the aforementioned discomfort symptoms." Additionally, this calculates out to a oral dose 4.17 - 4.55 mg/Kg of 4-MP hydrochloride, preventing or amelioration of symptom in subjects with reduced or absent aldehyde dehydrogenase subtype 2. Within the specifications they have place the about limit up to 4.4 mg/Kg.

Claim 13 recites the method of claim 10 wherein about 1 milligram to about 4 milligrams of 4-MP per kilogram of subject body mass is administered.

The 620 application these elements on Page 4 (label 118) of application "in three adult males, known to exhibit facial flushing and discomfort symptoms such as tachycardia, palpitations and headache upon drinking….. 55 to 60 kg..... orally administered 250 mg of 4-methylpyrazole hydrochloride dissolved in 50 ml water …….. 15 minutes before administration of 150 ml of sake…….they were observed for symptoms for a period of two hours after the start of drinking …….. they hardly exhibited any facial flushing and did not develop the aforementioned discomfort symptoms."

Additionally, the range stated in the "620 publication" calculates out to a oral dose 4.17 - 4.55 mg/Kg of 4-MP hydrochloride, preventing or amelioration of symptom in subjects with reduced or absent aldehyde dehydrogenase subtype 2. Within the specifications they have place the about limit up to 4.4 mg/Kg.

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Japanese patent application S57-106620(5) in view of Casavant et al., Pediatrics, Vol. 107 No. 1 January 2001. .

The limitations of claim 1 have been discussed supra in the 102 rejection over the '620 application.

The ‘620 application does not teach administration of 4-MP during or after alcohol consumption (claim 6) or the form of 4-MP in free base form (claim 2).

However, Casavant et al., teaches specifically states the use of the free base form of 4-MP which has the trade name Fomepizole (Antizol). Furthermore, Casavant teaches there is direct reference to treatment of pediatrics patients who have just consumed ethanol or after the subject has consumed ethanol.

Therefore, it would have prima facie obvious to one of ordinary skill in the art at the time invention was made to use the free base form of 4-MP to treat patients after the have consumed alcohol as taught by Casavant et al., in the method of the ‘620 application because it is well known that the free base form of 4-MP is an art recognized equivalent of 4-MP HCl and furthermore Cassavant et al., teaches effective treatment of pediatric patients after the have consumed alcohol with 4-MP.

In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed pharmaceutical agents are functionally different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ2d (PTO Bd. Pat. App. & Int. 1989).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DAVID WEBSTER whose telephone number is (571) 270-7675. The examiner can normally be reached on Monday through Thursday, 8:30 am - 5:00 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on (571) 272-00847. The fax phone number for the organization where this application or proceeding is Patent Application Information Retrieval (PAIR) system.

Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DDW/

Patent Examiner

/Patrick J. Nolan/

Supervisory Patent Examiner, Art Unit 4121